

October 14, 1949.

Dr. Harriett E. Taylor,
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Dear Harriett:

As you may imagine, I've read your last couple of papers with intense interest. I was a little surprised to read your introductory paragraph in your JEM paper, that "there has been little reason to believe that the bacterial cell contains a special genetic substance....", even as a manner of speaking, not so much from the outlook of my own work, but from the most general considerations. Such things as flagellae, adaptive enzymes, surface antigens in streptococci and pneumococci, which can be stripped off, or otherwise made to appear or disappear temporarily, speak conclusively for genetic material, along the lines of Muller's argument in his Pilgrim lecture. Because the very problem of inheritance is still unfamiliar to so many bacteriologists, I am sorry to see any concession made along these lines.

Lately, Esther and I have found that E. coli K-12 is lysogenic, which was quite a surprise at first, because we had been unable to detect the lysogenic phage until we accidentally isolated a sensitive, disinfected clone from K-12 which we could use as a detector strain. This finding impressed us with the familiar, but too often ignored fact that lysogenicity is exceedingly common, especially among enteric bacteria, and staphylococci, but may often be undetected because the lysogenic bacteria show no symptoms of infection, are very rarely disinfected, and a specific detector strain is necessary. The K-12 lysogenic phage, which we call lambda, does not appreciably influence the action of the T phages, but a phage, p20, has been isolated from sewage which is interfered with by lambda, although not itself lysogenic. Resistance to p20 is also conferred by the $\phi 6$ (V_6^r) mutation, so that, in a sense, lambda is an infective hereditary factor which mimics the action of the mutation, V_6^r . A good many people have been struck with the parallelism between lysogenicity, and transformation, and I am strongly inclined to (Sonneborn's) the point of view that the easiest way to assimilate transformation is to regard it as infection with an agent which remains autonomous within the "cytoplasm" of the cell, rather than as a "directed mutation" of a chromosome-localised gene. One of the questions which this viewpoint urgently demands a response to is the range of characters which can be controlled by the cytoplasmic system. I was a little jolted to read Austrian and McLeod's account of protein transformations (is this, by the way, the same as your ER - R ?), and now I wonder how wide the range is going to be. The only other character of which a test has been reported in the literature seems to be rabbit virulence, which is not

transformed. Have you tested other characters, and not published owing to negative results? Drug resistance might perhaps be a suitable one.

We were very distressed to learn of Andre Boivin's death. Ed Tatum and I had been trying to get in touch with him for the past two years, but it was only recently that we learned of his illness. Boivin had apparently made some mixup in the strains of E. coli C1-C2 that he brought to the US in '46, because we were both unable to duplicate his experiments, and the cultures we had disagreed in respect to various cultural characteristics from his descriptions.

Concerning your JEM paper, there were a couple of points that I perhaps did not completely understand. The first has to do with the examination of TP from the 2-step transformed S-III-N. I got the impression that the source cultures for this TP had all been obtained by the action of TP-N on III-1 and not by the action of TP-2 on III-1. If this is true, then the only "interaction" that need be postulated is competitive, because the experiment would then show that TP-N can displace TP-1. Have you examined the TP obtained from TP-2 on III-1 to determine whether it is ~~heterozygous~~ a mixture? Parenthetically, if TP-1 + TP-2, in the bacterial cell, can interact to produce TP-N, I would say that this specifically points to their non-allelism, if the concept can be applied at all. But I don't know how you would be able to rule out subsequent "mutations" to TP-N which would then displace -1 and -2.

If I am going to accept competition, it may be arguing the other way round, but may I discuss your conclusions (p. 417-8) that the action of TP-N on III-1 is not due to rare R variants. Firstly, although itself is a critical point, the citation for the inhibition by antiserum is a personal communication, so that the details are not available. But beyond that, the background experiment involved the inclusion of III antiserum into a system consisting mostly of R cells. In your system, you have a large number of cells which contain SIII and which might absorb most or all of the antibody. I would think that the mechanism of the inhibition would have to be worked out in more detail.

In a last ditch attempt to preserve the notion that ER, for example, is a deficiency in R, I would like to raise the improbability that the TP-ER is the (or a) substance with which TP-R combines within the cell. Then, R might be expected to mutate occasionally to ER, by "attenuation", and that this could be greatly accelerated by the competition for TP-R by TP-ER as against the TP-ER in the cells. This might be tested by studying the effects of TP-ER on the concomitant transformation of ER cells by TP-R.

I hope that you will take this criticism in the friendly and respectful spirit in which it is offered, as a token of ~~the~~ interest and admiration in your work. I mentioned the point about the test for heterozygosity of TP from III-R/-1/-N in an addition in proof to an MS for Ann. Rev. Microb. 1949, but doubt that it was sent in on time.

After all this, I don't dare say anything about my own work for fear of having it chopped off at the neck. We are still working on the diploid heterozygotes which constitute a fair fraction of the prototrophs isolated from certain crosses in K-12. There seems to be a regular elimination, at meiosis, of a chromosomal segment, which includes loci governing maltose-fermentation, galactose-fermentation, and streptomycin resistance, from the chromatids contributed by some parental stocks. Except that only a segment is involved, the ~~be~~ something like Auerbach's unstable centromere. I don't know yet ~~clarity~~ affects all K-12 stocks, or just those so far used.

A lot of minor difficulties came up which hindered testing the matter, but they should be cleared up soon. Max Zelle, at Cornell now, has been doing single cell pedigree studies on the segregation of the heterozygotes, but the results make it appear that segregation in multinucleate diploid cells (which are cytologically very plain) occurs dissynchronously, so that it is impossible to analyse the pedigrees in terms of single nuclear events. However, he does find the numerous lethal segregants demanded by the published interpretation of the disturbed numerical ratios, but single [multinucleate] cells are capable of dividing (or of trividing— splitting into 3 daughters simult!) into sister haploid and diploid cells. The most important point is ~~however~~, however, conclusively established: the segregations are incontestably from single cells. The segregation data leave no question of linkage, but further detailed proofs of linearity are a little confused the the segmental elimination (if that is what it is) that I mentioned earlier.

You may have heard about Cavalli's working on K-12 at Cambridge. He discovered an Hfr mutant— high frequency of recombination— from which I had thought at first to be able to obtain segregating zygote colonies without selection. But it turns out that, while his Hfr does have a greatly enhanced rate of zygote formation, that it is still not so high that, as a practical matter, selection for prototrophs or the like can be dispensed with. Cavalli has also found another coli strain (BTCC 123, E. coli "lactici-acidi") which crosses with K-12, and lately I have found another coli strain which seems pretty definitely now to be recombining, but is in a distinct mating system from K-12.

My lab. here is finally organized— not very large, but comfortably arranged and equipped, with enough room and funds for a couple of students, working on recombination in Salmonella (very encouraging) and the cytology of the diploids. This semester, I am first giving a lecture course on microbial genetics, primarily for majors in bacteriology, and therefore at a rather elementary level. But they are doing very well. Esther is finishing her thesis on genetic effects on relative mutability of alleles at the *Lac* locus. I hope that you will not forget to write and let me know how you are getting along.

With best regards,

Sincerely,

Joshua Lederberg